Clinical Information

Bystolic™
(nebivolol)

Section 2: Supporting Clinical and Economic Information

Section 2.1: Summaries of Key Clinical and Economic Studies

Clinical Study Report CSR NEB-302

Reference citation: Sherry JH, Miller AB. A Double-Blind, Multi-Center, Randomized, Placebo-Controlled, Parallel Group Dosing Study Evaluating the Effects of Nebivolol on Blood Pressure in Patients with Mild to Moderate Hypertension (Final Report), Bertek Pharmaceuticals Inc. Clinical Study Report NEB-302, Morgantown, West Virginia, February 2004.[93]

Principal findings

- Nebivolol at doses 1.25 to 40 mg effectively lowered BP in mild to moderate hypertensive patients.
- The following BP results are presented as least squares (LS) mean values.
- At study end (day 84), the baseline-adjusted reductions in trough SiDBP were 8.0, 8.5, 8.4, 9.2, 9.8, and 11.2 mm Hg for nebivolol 1.25, 2.5, 5, 10, 20, and 40 mg, respectively, compared with 2.9 mm Hg for placebo. The effects of nebivolol on SiDBP were significantly greater than with placebo (P <0.001 for all doses).
- The corresponding reductions in trough SiSBP for nebivolol 1.25, 2.5, 5, 10, 20, and 40 mg were 4.4, 6.3, 5.9, 7.0, 6.5, and 9.5 mm Hg, respectively, compared with a 2.2 mm Hg increase with placebo. The effects of nebivolol on SiSBP were significantly greater than with placebo (P = 0.002 for nebivolol 1.25 mg; P <0.001 for all other doses).
- Compared with placebo, the significant reductions in BP were apparent by week 2 (first assessment following randomization), and were sustained throughout the remainder of the 12-week treatment period.
- In addition, all doses of nebivolol were statistically significantly more effective than placebo in reducing peak sitting DBP (range, -9.1 to -13.9 mm Hg vs -5.4 mm Hg with placebo; P = 0.005 for nebivolol 1.25 mg and P <0.001 for all other doses) and SBP (range, -7.6 to -14.0 mm Hg vs -3.1 mm Hg with placebo; P = 0.029 and P = 0.015 for nebivolol 1.25 and 2.5 mg, respectively, and P <0.001 for all other doses).
- Reductions in DBP and SBP at trough and peak in both the standing and supine positions at doses of 2.5 mg and above were statistically significantly better than with placebo (P <0.001 for most doses at most parameters).
- Compared with placebo, a significantly higher proportion of patients were responders in all nebivolol treatment groups. The response rates were 45.8%, 50.0%, 50.3%, 53.6%, 59.6%, and 64.5% with nebivolol 1.25, 2.5, 5, 10, 20, and 40 mg, respectively, compared with 24.7% with placebo

(*P* = 0.008 for nebivolol 1.25 mg; *P* = 0.001 for nebivolol 2.5 mg; and *P* <0.001 for all other doses).

- Placebo-subtracted trough-to-peak ratios for the reduction in sitting DBP from baseline to the end of treatment were 0.9 or above for all doses of nebivolol, confirming once-daily dosing was appropriate.
- Mean heart rate decreased significantly from baseline in patients treated with nebivolol, and this reduction was significantly different from placebo. From baseline, mean trough sitting heart rate decreased by -1.4, -2.4, -4.9, -5.5, -7.9, and -8.9 bpm with nebivolol 1.25, 2.5, 5, 10, 20, and 40 mg, respectively, compared with a 2.4 bpm increase with placebo. These decreases were dose-dependent and were statistically significant at all doses (*P* = 0.002 for nebivolol 1.25 mg and *P* <0.001 for all other doses).
- Nebivolol was well tolerated. A total of 23/909 (2.5%) patients withdrew from this study due to AEs. Of these patients, 22 were taking nebivolol, and 2 of those withdrew due to pretreatment-emergent AEs.
- The overall incidence of treatment emergent adverse events (TEAEs) in the nebivolol (382/828 patients; 46.1%) and placebo (33/81 patients; 40.7%) groups was comparable (*P* = 0.273). However, AEs tended to increase slightly by nebivolol dose, ranging from 34.9% in the 1.25 mg treatment group to 50.6% in the 40 mg group. When each nebivolol treatment group was evaluated separately, only patients treated with nebivolol 20 and 40 mg had a significantly higher incidence of AEs (*P* <0.044 and *P* <0.009, respectively).
- Among all patients taking nebivolol, the most common TEAEs (reported by >2%) were headache (7.1%), fatigue (3.6%), nasopharyngitis (2.9%), diarrhea (2.8%), dizziness (2.8%), and increased CRP (2.7%). However, none of these adverse events was dose-related.
- The incidence of AEs commonly associated with beta blocker use was low in the combined nebivolol group (all doses), including fatigue (3.6% vs 2.5% with placebo), dyspnea (1.0%), bradycardia (0.7%), erectile dysfunction (0.2%), and depression (0.2%).
- There were no deaths reported in this study. Eleven patients in the nebivolol group and one in the placebo group experienced serious adverse events during the double-blind treatment period. Of the 11 serious AEs in the nebivolol, 2 were considered possibly drug-related: 1 patient on nebivolol 20 mg had an abnormal electrocardiogram (ECG) with inferior T wave changes and another patient on nebivolol 40 mg had an abnormal ECG with ST changes. However, both resolved spontaneously without discontinuation of study treatment.
- Nebivolol treatment was not associated with any significant changes in any of the laboratory parameters associated with cardiovascular risk (ie, total cholesterol, LDL-C, triglycerides, and glucose), except for HDL-C which showed small, but statistically significant decreases from baseline (mean decrease from 0.383-1.887 mg/dL across the dose range)

compared with placebo (P = 0.005 and P = 0.017 for nebivolol 1.25 and 2.5 mg, respectively, and P <0.001 for nebivolol 5, 10, 20, and 40 mg).

Implications of study findings

- Once-daily nebivolol is an effective antihypertensive in the treatment of mild to moderate hypertension in a demographically heterogeneous population (43.0% were women, 14.5% were black, 21.2% were aged 65 years or older, 9.7% were diabetic, and 43.9% were moderately obese).
- Nebivolol is also well tolerated, with a low incidence of AEs such as fatigue, dyspnea, bradycardia, sexual dysfunction, and depression that are associated with many beta blockers.
- Nebivolol treatment is not associated with adverse effects on serum total cholesterol and LDL-C levels and is associated with neutral effects on serum glucose levels.
- In conclusion, the efficacy and safety demonstrated by nebivolol in this study, coupled with the unique hemodynamic profile and NO-mediated vasodilatory properties documented for this agent may provide benefits beyond simple blood pressure lowering in patients with mild to moderate hypertension.

Study Population: Male and female patients aged 18 years or older with mild to moderate hypertension, defined as mean SiDBP ≥95 mm Hg and ≤109 mm Hg, were eligible to participate in the study. Patients were not included if they had secondary or malignant hypertension; BMI ≥35 kg/m^2; bronchospasm, bradycardia, or any other known contraindication to beta blocker therapy; uncontrolled diabetes mellitus (hemoglobin A_{1c} ≥10%); recent (within 6 months) myocardial infarction or stroke; heart failure; hemodynamically significant valvular heart disease; clinically significant thyroid, renal, or hepatic dysfunction; peripheral vascular disease; positive pregnancy test result; previous exposure to nebivolol; or concomitant therapy with at least 1 prohibited or restricted medication that may have affected BP (eg, all antidepressants with BP-altering effects, including tricyclic antidepressants and monoamine oxidase inhibitors).

Patients were stratified across all treatment arms by nebivolol metabolism based on oxidative genotype (extensive vs poor metabolizers), history of diabetes mellitus, self-reported race (black vs nonblack), age (younger than 65 vs 65 years or older), and sex.

Study Design and Procedures: This phase 3, double-blind, randomized, placebo-controlled, parallel-group study was conducted at 70 sites in the United States from September 2001 (date of first enrollment) to March 2003 (date last patient completed study).

At the screening visit, patients were examined and a medical history was obtained to determine patients' eligibility for enrollment in the study. Following screening, all patients entered a 4-week, single-blind placebo run-in/washout phase. Patients previously on antihypertensive medication were allowed an additional 2-week single-blind placebo run-in/washout. At the end of the placebo run-in/washout period (day 0), baseline and demographic characteristics were recorded and eligible patients were randomized to receive placebo or once-daily nebivolol 1.25, 2.5, 5, 10, 20, or 30/40 mg in a double-blind manner for 84 days. Patients in the 30/40 mg nebivolol group were initiated at 30 mg once daily; the dosage was increased to 40 mg once daily after 2 weeks, only if their sitting heart rate at trough was >55 beats per minute (bpm); otherwise, these patients remained on 30 mg once daily. Patients returned to the study unit for assessments on days 14, 28, 56, and 84 of the double-blind treatment period, at which time BP and heart rate were measured, compliance with study medication was monitored, and use of concomitant medications was recorded. Clinical laboratory parameters were measured at screening, at randomization, and at day 84.

Concomitant therapy with oral and ophthalmic beta blockers, angiotensin-converting enzyme inhibitors, angiotensin II receptor blockers, CCBs, diuretics, and alpha$_1$-receptor blockers was prohibited during the single-blind run-in phase and during the double-blind treatment period.

Primary and Secondary End Points: The primary efficacy end point was change from baseline to day 84 in mean SiDBP at trough (24±2 hours post-previous morning's dose). Secondary efficacy end points included changes from baseline to day 84 in mean SiSBP at trough, mean SiDBP and SiSBP at peak (2-3 hours postdose), and mean supine and standing DBP and SBP at trough and peak. Another efficacy variable was the responder rates of treatment groups, defined as the proportion of patients with an SiDBP <90 mm Hg at the end of the study or an absolute reduction of ≥10 mm Hg in SiDBP from baseline.

Efficacy and Safety Assessments: BP was measured at trough and peak using an automatic sphygmomanometer and appropriately sized cuff in the supine, sitting, and standing positions. Three separate measurements were taken 2 minutes apart in the same arm: first after the patient had been at rest in the supine position for at least 5 minutes, then after sitting for 1 minute, and finally after standing for 1 minute. The mean of 3 readings in each position was calculated and recorded. Trough BP and heart rate measurements were taken at screening and randomization and on days 14, 28, 56, and 84 of the treatment period; peak BP and heart rate measurements were taken at randomization and on days 28 and 84 of the treatment period. Safety was assessed by clinical review, vital signs (including heart rate), 12-lead ECGs, and clinical laboratory evaluations including chemistry panel, hematologic profile, and urinalysis. All AEs occurring during the study were documented as to type, onset, duration, intensity, and relation to study drug.

Statistical methods: Data were analyzed using the intent to treat approach and LOCF method was used in the case of missing data. Two sided statistical tests were performed, with a significance level of 0.05.

The patients' demographic characteristics and vital signs at baseline were summarized and compared between the treatment groups. Data for continuous variables were compared using analysis of variance overall *F* test. For categoric variables, the observed frequencies were compared using a chi-square test. Changes in BP from baseline to the last visit (day 84) were compared between treatment groups using an analysis of covariance (ANCOVA) model with treatment as a main effect and with baseline BP and dichotomous variables as covariates. Baseline dichotomous covariates included age group (<65 vs ≥65), race (black vs nonblack), sex, diabetes (history of diabetes mellitus vs no history of diabetes mellitus), obesity (BMI <35 kg/m^2 or $\geq$30 kg/m^2) and metabolism of nebivolol (extensive metabolizer vs poor metabolizer). The primary statistical method was a step-down dose-response trend test using a linear contrast in the ANCOVA. The changes from baseline in the continuous efficacy variables were summarized by n, mean, standard deviation, Least Squares (LS) mean, LS standard error, and p-value for the step-down trend test. If the test for trend was significant ($P \leq 0.05$), the LS mean difference of that particular treatment versus placebo, the 95% confidence interval around this difference and the p-value for this comparison were displayed. The 30/40 mg dose was studied for safety purposes and therefore was not included in the step-down trend test for efficacy. Response rates were analyzed using a logistic regression model with responder as the response variable and baseline DBP and dichotomous variables as covariates; the frequencies were compared using the Wald chi-square test.

For continuous safety variables, the change from baseline was tested with a step-down method similar to that used for the efficacy variables, using an ANCOVA model with treatment and baseline covariates, except that linear contrasts comprised all treatment groups, including the 40 mg group. For categoric safety variables, the *P* value was based on the Cochran-Mantel-Haenszel test adjusted for dichotomous baseline covariates. The overall AE incidences were compared for each individual nebivolol dose group and for all dose groups combined versus placebo.

Sample characteristics: A total of 1573 patients were screened; 278 patients failed screening and 1295 patients continued in the single-blind phase. The ITT population consisted of 81, 83, 82, 165, 166, 166, and 166 patients who took at least one dose of placebo or nebivolol 1.25, 2.5, 5, 10, 20, or 30/40 mg, respectively. Of the 166 patients randomized to nebivolol 40 mg, 147 had their dose increased to 40 mg and 19 remained at 30 mg based on heart rate. A total of 777/909 (85.5%) patients completed the study; 82.7% in the placebo group and 85.7% in the nebivolol groups combined.

Compliance behavior: Patient compliance is shown in **Table 8**.

Table 8. Patient Compliance in Study NEB-302 (Population: Intent-to-Treat)

Statistic	Placebo	Nebivolol 1.25 mg n (%)	Nebivolol 2.5 mg n (%)	Nebivolol 5 mg n (%)	Nebivolol 10 mg n (%)	Nebivolol 20 mg n (%)	Nebivolol 30/40 mg n (%)
N	78	80	79	156	156	154	160
Non-compliance	2 (2.6)	3 (3.8)	1 (1.3)	6 (3.8)	7 (4.5)	3 (1.9)	5 (3.1)
Mean (SD)	99.1 (2.5)	98.6 (3.6)	98.9 (3.2)	98.6 (3.4)	98.0 (7.2)	98.6 (3.1)	98.5 (3.6)
Median	100.0	100.0	100.0	100.0	100.0	100.0	100.0
Range	(86.2, 100.0)	(75.0, 100.0)	(77.6, 100.0)	(74.1, 100.0)	(33.3, 100.0)	(77.6, 100.0)	(69.4, 100.0)

(a) A patient is compliant if 90% or more scheduled doses were taken.

(b) *P* = 0.807 (Chi-Square Test).

Note: If any bottle was not returned or the number of pills returned not recorded, then the patient will be excluded from the overall compliance. Compliances greater than 100% were set to 100%.

Generalizability of population treated: The composition of the study population was as follows: 43.0% were women, 14.5% were black, 21.2% were aged 65 years or older, 9.7% were diabetic, and 43.9% were obese (moderately). Therefore, the patients studied can be regarded as representative of the general U.S. hypertensive population.[94-97]

CSR NEB-305

Reference citation: Sherry JH, Miller AB. A Double-Blind, Multi-Center, Randomized, Placebo-Controlled, Parallel Group Study of the Effects of Nebivolol on Safety and Efficacy in Patients with Mild to Moderate Hypertension (Final Report), Bertek Pharmaceuticals Inc. Clinical Study Report NEB-305, Morgantown, West Virginia, February 2004.[98]

Principal findings

- Nebivolol at doses 5, 10, and 20 mg effectively lowered BP in mild to moderate hypertensive patients.
- The following BP results are presented as LS mean values.
- At study end (day 84), the baseline-adjusted reductions in trough SiDBP were 7.8, 8.5, and 9.1mm Hg for nebivolol 5, 10, and 20 mg, respectively, compared with 4.6 mm Hg for placebo. The effects of nebivolol on SiDBP were significantly greater than with placebo (P = 0.002 for nebivolol 5 mg; P <0.001 for the other doses).
- The corresponding reductions in trough SiSBP for nebivolol 5, 10, and 20 g were 4.2, 3.5, and 6.7 mm Hg, respectively, compared with a 0.4 mm Hg decrease with placebo. The effects of nebivolol on SiSBP were significantly greater at 20 mg than with placebo (P <0.001).
- Compared with placebo, greater reductions in BP were apparent by week 2 (first assessment following randomization), and were sustained throughout the remainder of the 12-week treatment period.
- In addition, nebivolol was statistically significantly more effective than placebo in reducing peak sitting DBP at all doses (range, -10.5 to -12.2 mm Hg vs -7.0 mm Hg with placebo; P <0.001 for all doses) and SBP at the 10 and 20 mg doses (-9.5 and -10.7 mm Hg, respectively, vs -4.7 mm Hg with placebo; P = .004 for nebivolol 10 mg and P <0.001 for nebivolol 20 mg).
- Reductions in standing and supine DBP from baseline to end of study were statistically significant for all doses of nebivolol (5, 10, and 20 mg) at peak and trough (P <0.001 for most doses at most parameters). At trough, statistically significant reductions in standing (P = 0.002) and supine (P <0.001) SBP were observed from baseline to end of study for nebivolol 20 mg; at peak, statistically significant reductions in standing (P = 0.005 for 5 mg and P <0.001 for the other 2 doses) and supine (P = 0.002 for 5 mg and P <0.001 for the other 2 doses) SBP from baseline to end of study were shown for all nebivolol doses.
- Compared with placebo, a significantly higher proportion of patients were responders in all nebivolol treatment groups. The response rates were 66.0%, 66.8%, and 68.9% with nebivolol 5, 10, and 20 mg, respectively, compared with 49.3% with placebo (P = 0.009 for nebivolol 5 mg; P = 0.005 for nebivolol 10 mg; and P = 0.002 for nebivolol 20 mg).

- Placebo-subtracted trough-to-peak ratios for the reduction in sitting DBP from baseline to the end of treatment ranged from 0.8 to 0.9 for all doses of nebivolol, confirming once-daily dosing was appropriate.
- Mean heart rate decreased significantly from baseline in patients treated with nebivolol, and this reduction was significantly different from placebo. From baseline, mean trough sitting heart rate decreased by -5.1, -6.5 and -7.2 bpm with nebivolol 5, 10, and 20 mg, respectively. These decreases were dose-dependent and were statistically significant at all doses (*P* <0.001 for all doses).
- Nebivolol was well tolerated. Most adverse events were mild or moderate in intensity. Twenty-two patients withdrew due to treatment emergent adverse events (4, 3, 8, and 7 patients on placebo and nebivolol 5, 10, and 20 mg, respectively) and 2 additional patients withdrew during treatment due to pre-treatment emergent adverse events.
- Incidences of AEs were comparable in the placebo and nebivolol 5- and 10 mg treatment groups (36.0%, 39.3%, and 39.8%, respectively); however, there was a statistically significant increase in AE incidence in patients taking nebivolol 20 mg (48.4%) compared with placebo (36.0%) (*P* = 0.028).
- Among all patients taking nebivolol, the most common TEAEs were headache (7.5%), fatigue (3.8%), and nasopharyngitis (3.7%).
- The incidence of AEs commonly associated with beta blocker use was low in the combined nebivolol group (all doses) and consisted of fatigue (3.8% vs 1.3% with placebo) and bradycardia (0.8%).
- There were no deaths reported in this study. Seven serious adverse events were reported during double-blind treatment. The events occurred in 6 patients taking nebivolol (2 patients for each dose), and 3 of the events were considered possibly drug related: shortness of breath, myocardial infarction, and ruptured aortic aneurysm. These AEs resulted in withdrawal of patients from the trial. SAEs not considered related to study medication consisted of heart failure with severe coronary artery disease, deep-vein thrombosis, and leucopenia.
- Nebivolol treatment was not associated with any significant changes in any of the laboratory parameters associated with cardiovascular risk (ie, total cholesterol, LDL-C, triglycerides, and glucose), except for HDL-C. There were small decreases in HDL-C for all doses, which reached statistical significance for nebivolol 10 and 20 mg. (For the 10 and 20 mg doses, mean differences from placebo were -2.76 and -2.62 mg/dL, respectively).

Implications of study findings

- Once-daily nebivolol lowers BP effectively in a demographically heterogenous population of patients (46.5% women, 13.0% black, 18.2% aged 65 years or older 40% moderately obese, 4.6% diabetic) with mild to moderate hypertension.
- Nebivolol is safe and well tolerated, with a low incidence of AEs typically associated with beta blocker treatment, such as fatigue, dyspnea, bradycardia, sexual dysfunction and depression.
- Nebivolol treatment is associated with neutral effects on the metabolic parameters of serum total cholesterol, LDL-C, and serum glucose.
- In conclusion, these efficacy and safety data support nebivolol—a novel beta blocker that combines highly selective β_1-blockade with endothelium-dependent vasodilation—as a valuable therapeutic option for patients with mild to moderate hypertension.

Study Population: Male and female patients aged 18 years or older with mild to moderate hypertension, defined as mean SiDBP $\geq$95 mm Hg and $\leq$109 mm Hg, were eligible to participate in the study. Patients were not included if they had secondary or malignant hypertension; BMI $\geq$35 kg/m^2; bronchospasm, bradycardia, or any other known contraindication to beta blocker therapy; uncontrolled diabetes mellitus (hemoglobin A_{1c} $\geq$10%); recent (within 6 months) myocardial infarction or stroke; heart failure; hemodynamically significant valvular heart disease; clinically significant thyroid, renal, or hepatic dysfunction; peripheral vascular disease; positive pregnancy test result; previous exposure to nebivolol; or concomitant therapy with at least 1 prohibited or restricted medication that may have affected BP (eg, all antidepressants with BP-altering effects, including tricyclic antidepressants and monoamine oxidase inhibitors).

Patients were stratified across all treatment arms by nebivolol metabolism based on oxidative genotype (extensive vs poor metabolizers), history of diabetes mellitus, self-reported race (black vs nonblack), age (younger than 65 years vs 65 years or older), and sex.

Study Design and Procedures: This phase 3, double-blind, randomized, placebo-controlled parallel-group study was conducted at 89 sites in the United States and Europe from September 2001 (date of first enrollment) to March 2003 (date last patient completed study).

At the screening visit, patients were examined and a medical history was obtained to determine patients' eligibility for enrollment in the study. Following screening, all patients entered a 4-week, single-blind placebo run-in/washout phase. Patients previously on antihypertensive medication were allowed an additional 2-week single-blind placebo run-in/washout. At the end of the placebo run-in/washout period (day 0), baseline and demographic characteristics were recorded and eligible patients were randomized to receive placebo or once-daily

nebivolol 5, 10, or 20 mg in a double-blind manner for 84 days. Patients returned to the study unit for assessments on days 14, 28, 56, and 84 of the double-blind treatment period, at which time BP and heart rate were measured, compliance with study medication was monitored, and use of concomitant medications was recorded. Clinical laboratory parameters were measured at screening, at randomization, and at day 84.

Concomitant therapy with oral and ophthalmic beta blockers, angiotensin-converting enzyme inhibitors, angiotensin II receptor blockers, CCBs, diuretics, and alpha$_1$-receptor blockers was prohibited during the single-blind run-in phase and during the double-blind treatment period.

Primary and Secondary End Points: The primary efficacy end point was change from baseline to day 84 in mean SiDBP at trough (24±2 hours post-previous morning's dose). Secondary efficacy end points included changes from baseline to day 84 in mean SiSBP at trough, mean SiDBP and SiSBP at peak (2-3 hours postdose), and mean supine and standing DBP and SBP at trough and peak. Another efficacy variable was the responder rates of treatment groups, defined as the proportion of patients with an SiDBP <90 mm Hg at the end of the study or an absolute reduction of ≥10 mm Hg in SiDBP from baseline.

Efficacy and Safety Assessments: BP was measured at trough and peak using an automatic sphygmomanometer and appropriately sized cuff in the supine, sitting, and standing positions. Three separate measurements were taken 2 minutes apart in the same arm: first after the patient had been at rest in the supine position for at least 5 minutes, then after sitting for 1 minute, and finally after standing for 1 minute. The mean of 3 readings in each position was calculated and recorded. Trough BP and heart rate measurements were taken at screening and randomization and on days 14, 28, 56, and 84 of the treatment period; peak BP and heart rate measurements were taken at randomization and on days 28 and 84 of the treatment period. Safety was assessed by clinical review, vital signs (including heart rate), 12-lead ECGs, and clinical laboratory evaluations including chemistry panel, hematologic profile, and urinalysis. All AEs occurring during the study were documented as to type, onset, duration, intensity, and relation to study drug.

Statistical methods: Data were analyzed using the intent to treat approach and LOCF method was used in the case of missing data.

The patients' demographic characteristics and vital signs at baseline were summarized and compared between the treatment groups. Data for continuous variables were compared using analysis of variance overall *F* test. For categoric variables, the observed frequencies were compared using a chi-square test. Changes in BP from baseline to the last visit (day 84) were compared between treatment groups using an analysis of covariance (ANCOVA) model with treatment as a main effect and with baseline BP and dichotomous variables as

covariates. Baseline dichotomous covariates included age group (<65 vs ≥65), race (black vs nonblack), sex, diabetes (history of diabetes mellitus vs no history of diabetes mellitus) and metabolism of nebivolol (extensive metabolizer vs poor metabolizer). The primary statistical method was a step-down dose-response trend test using a linear contrast in the ANCOVA. The changes from baseline in the continuous efficacy variables were summarized by n, mean, standard deviation, Least Squares (LS) mean, LS standard error, and p-value for the step-down trend test. If the test for trend was significant ($P \leq 0.05$), the LS mean difference of that particular treatment versus placebo, the 95% confidence interval around this difference and the p-value for this comparison were displayed. Response rates were analyzed using a logistic regression model with responder as the response variable and baseline DBP and dichotomous variables as covariates; the frequencies were compared using the Wald chi-square test.

For continuous safety variables, the change from baseline was tested with a step-down method similar to that used for the efficacy variables, using an ANCOVA model with treatment and baseline covariates, except that linear contrasts comprised all treatment groups, including the 40 mg group. For categoric safety variables, the *P* value was based on the Cochran-Mantel-Haenszel test adjusted for dichotomous baseline covariates. The overall AE incidences were compared for each individual nebivolol dose group and for all dose groups combined versus placebo.

Sample characteristics: A total of 1288 patients were screened (including 2 patients who were screened and counted twice); 150 patients failed screening and 1138 patients continued in the single-blind phase. The ITT population consisted of 75, 244, 244, and 244 patients who took at least one dose of placebo or nebivolol 5, 10, or 20 mg, respectively. A total of 702/807 (87.0%) patients completed the study; 81.3% in the placebo group and 87.6% in the nebivolol groups combined.

Compliance behavior: Patient compliance is shown in **Table 9**.

Table 9. Patient Compliance in Study NEB-305 (Population: Intent-to-Treat)

Statistic	Placebo	Nebivolol 5 mg n (%)	Nebivolol 10 mg n (%)	Nebivolol 20 mg n (%)
N	74	232	230	237
Compliance[a,b]	67 (90.5)	218 (94.0)	212 (92.2)	224 (94.5)
Non-compliance	7 (9.5)	14 (6.0)	18 (7.8)	13 (5.5)
Mean (SD)	97.2 (6.4)	97.4 (6.6)	97.4 (5.7)	97.7 (4.3)
Median	100.0	100.0	100.0	100.0
Range	(58.0, 100.0)	(50.0, 100.0)	(61.3, 100.0)	(75.0, 100.0)

(a) A patient is compliant if 90% or more scheduled doses were taken.

(b) *P* = 0.555 (Chi-Square Test).

Note: If any bottle was not returned or the number of pills returned not recorded, then the patient will be excluded from the overall compliance. Compliances greater than 100% were set to 100%.

Generalizability of population treated: The composition of the study population was as follows: 46.5% were women, 13.0% were black, 18.2% were aged 65 years or older, 4.6% were diabetic (a smaller percentage than in NEB-302), and 40.1% were obese (moderately). Therefore, the patients studied can be regarded as representative of the general U.S. hypertensive population.[94-97]

CSR NEB-202

Reference citation: Sherry JH, Miller AB. A Double-Blind, Multi-Center, Randomized, Placebo-Controlled, Parallel Group Dosing Study of the Effects of Nebivolol on Blood Pressure in Black Patients With Mild to Moderate Hypertension, Bertek Pharmaceuticals Inc. Clinical Study Report NEB-202, Morgantown, West Virginia, March 2004[69]

Principal findings

- Nebivolol effectively lowered BP in black patients with mild to moderate hypertension.
- The following BP results are presented as LS mean values.
- At study end (day 84), the baseline-adjusted reductions in trough SiDBP were 5.7, 7.7, 8.9, 8.9, and 8.3 mm Hg for nebivolol 2.5, 5, 10, 20, and 40 mg, respectively, compared with 2.8 mm Hg for placebo. The effects of nebivolol 5, 10, 20, and 40 mg on SiDBP were significantly greater than with placebo ($P = 0.004$ for nebivolol 5 mg; $P \leq 0.001$ for all other doses).
- The corresponding reductions in trough SiSBP for nebivolol 2.5, 5, 10, 20, and 40 mg were 1.9, 3.0, 6.4, 7.6, and 7.2 mm Hg, respectively, compared with a 0.4 mm Hg decrease with placebo. The effects of nebivolol 10, 20, and 40 mg on SiSBP were significantly greater than with placebo ($P = 0.045$ for nebivolol 10 mg; $P = 0.016$ for nebivolol 20 mg; and $P = 0.022$ for nebivolol 40 mg); as with SiDBP, the response to the 40 mg dose was not greater than those to the 10 and 20 mg doses.
- Compared with placebo, the significant incremental reductions in BP were apparent by week 2 (first assessment following randomization), and were sustained throughout the reminder of the 12-week treatment period.
- In addition, nebivolol was statistically significantly more effective than placebo in reducing peak sitting DBP at all doses (range, -8.6 to -12.3 mm Hg vs -3.8 mm Hg with placebo; $P = 0.008$ for nebivolol 2.5 mg and $P < 0.001$ for all other doses) and SBP at doses from 5 to 40 mg (range, -10.6 to -12.2 mm Hg vs -3.0 mm Hg with placebo; $P = 0.011$ for nebivolol 5 mg; $P = 0.005$ for nebivolol 10 mg; and $P = 0.002$ for nebivolol 20 and 40 mg).
- Mean changes in blood pressure for patients treated with nebivolol were superior to placebo at all doses for all DBP parameters and nearly all SBP parameters (although statistical significance not achieved in every instance, especially at the 2.5 mg dose).
- Compared with placebo, a significantly higher proportion of patients were responders in all nebivolol treatment groups ≥5 mg. The response rates were 58.0%, 58.8%, 64.0%, and 56.9% with nebivolol 5, 10, 20, and 40 mg, respectively, compared with 26.5% with placebo ($P = 0.002$ for nebivolol 5 mg; $P < 0.001$ for all other doses).

- All doses of nebivolol slowed heart rate. From baseline, mean trough sitting heart rate decreased by -4.4, -3.9, -7.2, -5.9, and -7.8 bpm with nebivolol 2.5, 5, 10, 20, and 40 mg, respectively, compared with a 2.4 bpm decrease with placebo. These decreases were statistically significant at 10, 20, and 40 mg ($P \leq 0.009$).
- Nebivolol was well tolerated. The overall incidence of treatment emergent adverse events (TEAEs) in the nebivolol (113/251 patients; 45.0%) and placebo (19/49 patients; 38.8%) groups was comparable ($P = 0.474$). Most TEAEs were mild in intensity and thought to be unrelated to the study drug.
- Among all patients taking nebivolol, the most common TEAEs (reported by >2%) were headache (5.6%), dizziness (3.6%), arthralgia (3.6%), diarrhea (3.2%), fatigue (2.8%), nasopharyngitis (2.4%), urinary tract infection (2.4%), constipation (2.0%), and chest pain (2.0%). No dose-related trend for the incidence of individual AEs was observed.
- The incidence of AEs commonly associated with beta blocker use was low in the combined nebivolol group (all doses), including fatigue (2.8% vs 0% with placebo), bradycardia (0.4%), decreased libido (0.4%), and dyspnea (0.4%).
- There were no deaths reported in this study. Four serious adverse events were reported during this study, 2 in the nebivolol 40 mg group (chest pain and bladder cancer) and 2 in the nebivolol 5 mg group (motor vehicle accident and cerebral hemorrhage). Cerebral hemorrhage was the only one of these events considered possibly related to the study drug.
- Five nebivolol-treated patients withdrew due to TEAEs (1, 1, 0, 1, and 2 patients taking nebivolol 2.5, 5, 20, and 40 mg, respectively) compared with no placebo-treated patients.
- For laboratory parameters associated with cardiovascular risk, nebivolol demonstrated statistically nonsignificant increases in serum glucose in all treatment groups. In most of the treatment groups, including the placebo group, statistically nonsignificant reductions in total and low-density lipoprotein cholesterol, as well as nonsignificant increases in triglycerides were observed. In addition, changes in high-density lipoprotein cholesterol occurred in all groups (–0.8 mg/dL with placebo and –3.2, –5.2, –1.4, –3.9 and –6.1 mg/dL with nebivolol 2.5, 5, 10, 20, and 40 mg, respectively); these reductions with nebivolol did not appear to be dose-related and were statistically significant only in the nebivolol 40 mg dose group ($P = 0.03$).

Implications of study findings

- Once-daily nebivolol is an effective antihypertensive in the treatment of black patients with mild to moderate hypertension.
- Nebivolol is also well tolerated, with an AE rate comparable to that of placebo. Patients treated with nebivolol had a low incidence of AEs such as fatigue, bradycardia, decreased libido, and dyspnea that are associated

with many beta blockers. These results may be relevant to patient compliance, which is often associated with tolerability.
- The findings that nebivolol had only a small (and nonsignificant) impact on glucose in this study and was generally not associated with adverse metabolic effects suggest that this agent may be a treatment option for patients with metabolic issues (ie, patients with diabetes or metabolic syndrome). The black population has a high incidence of diabetes.[99]
- Black hypertensive patients often exhibit endothelial dysfunction. Nebivolol with its unique hemodynamic profile and nitric oxide mediated vasodilatory properties within the endothelium may provide benefits beyond BP lowering in this patient population.
- In conclusion, nebivolol is safe and effective in lowering blood pressure in hypertensive black patients, a population that has been difficult to treat with beta blockers until now.

Study Population: Black male and female patients aged 18 years or older with mild to moderate hypertension, defined as mean SiDBP ≥95 mm Hg and ≤109 mm Hg, were eligible to participate in the study. Patients were not included if they had secondary or malignant hypertension; BMI ≥40 kg/m^2; bronchospasm, bradycardia, or any other known contraindication to beta blocker therapy; uncontrolled diabetes mellitus (hemoglobin A_{1c} ≥10%); recent (within 6 months) myocardial infarction or stroke; heart failure; hemodynamically significant valvular heart disease; clinically significant thyroid, renal, or hepatic dysfunction; peripheral vascular disease; positive pregnancy test result; previous exposure to nebivolol; or concomitant therapy with at least 1 prohibited or restricted medication that may have affected BP (eg, all antidepressants with BP-altering effects, including tricyclic antidepressants and monoamine oxidase inhibitors).

Patients were stratified across all treatment arms by nebivolol metabolism based on oxidative genotype (extensive vs poor metabolizers), history of diabetes mellitus, age (younger than 65 years vs 65 years or older), and sex.

Study Design and Procedures: This phase 3, double-blind, randomized, placebo-controlled parallel-group study was conducted at 39 sites in the United States from November 2001 (date of first enrollment) to August 2003 (date last patient completed study).

At the screening visit, patients were examined and a medical history was obtained to determine patients' eligibility for enrollment in the study. Following screening, all patients entered a 4-week, single-blind placebo run-in/washout phase. Patients previously on antihypertensive medication were allowed an additional 2-week single-blind placebo run-in/washout. At the end of the placebo run-in/washout period (day 0), baseline and demographic characteristics were recorded and eligible patients were randomized to receive placebo or once-daily nebivolol 2.5, 5, 10, 20, or 40 mg in a double-blind manner for 84 days. Patients returned to the study unit for assessments on days 14, 28, 56, and 84 of the

double-blind treatment period, at which time BP and heart rate were measured, compliance with study medication was monitored, and use of concomitant medications was recorded. Clinical laboratory parameters were measured at screening, at randomization, and at day 84.

Concomitant therapy with oral and ophthalmic beta blockers, angiotensin-converting enzyme inhibitors, angiotensin II receptor blockers, CCBs, diuretics, and $alpha_1$-receptor blockers was prohibited during the single-blind run-in phase and during the double-blind treatment period.

Primary and Secondary End Points: The primary efficacy end point was change from baseline to day 84 in mean SiDBP at trough (24±2 hours post-previous morning's dose). Secondary efficacy end points included changes from baseline to day 84 in mean SiSBP at trough, mean SiDBP and SiSBP at peak (2-3 hours postdose), and mean supine and standing DBP and SBP at trough and peak. Another efficacy variable was the responder rates of treatment groups, defined as the proportion of patients with an SiDBP <90 mm Hg at the end of the study or an absolute reduction of ≥10 mm Hg in SiDBP from baseline.

Efficacy and Safety Assessments: BP was measured at trough and peak using an automatic sphygmomanometer and appropriately sized cuff in the supine, sitting, and standing positions. Three separate measurements were taken 2 minutes apart in the same arm: first after the patient had been at rest in the supine position for at least 5 minutes, then after sitting for 1 minute, and finally after standing for 1 minute. The mean of 3 readings in each position was calculated and recorded. Trough BP and heart rate measurements were taken at screening and randomization and on days 14, 28, 56, and 84 of the treatment period; peak BP and heart rate measurements were taken at randomization and on days 28 and 84 of the treatment period. Safety was assessed by clinical review, vital signs (including heart rate), 12-lead ECGs, and clinical laboratory evaluations including chemistry panel, hematologic profile, and urinalysis. All AEs occurring during the study were documented as to type, onset, duration, intensity, and relation to study drug.

Statistical methods: Data were analyzed using the intent to treat approach and LOCF method was used in the case of missing data.

Background and demographic data were summarized using descriptive statistics, and homogeneity was assessed using analysis of variance overall *F* test for continuous variables and the chi-square test for categoric variables. To test for treatment differences, continuous efficacy variables were analyzed using an analysis of covariance (ANCOVA) model with treatment as a main effect and with baseline BP and dichotomous variables as covariates. Baseline dichotomous covariates included age group (<65 vs ≥65), sex, diabetes (history of diabetes mellitus vs no history of diabetes mellitus) and metabolism of nebivolol (poor metabolizer vs extensive metabolizer). The primary statistical method was a

step-down dose-response trend test using a linear contrast in the ANCOVA. The changes from baseline in the continuous efficacy variables were summarized by n, mean, standard deviation, Least Squares (LS) mean, LS standard error, and p-value for the step-down trend test. If the test for trend was significant (P $\leq$0.05), the LS mean difference of that particular treatment versus placebo, the 95% confidence interval around this difference and the p-value for this comparison were displayed. The 40 mg dose was studied for safety purposes and therefore was not included in the step-down trend test for efficacy. Response rates were analyzed using a logistic regression model with responder as the response variable and baseline DBP and dichotomous variables as covariates; the frequencies were compared using the Wald chi-square test.

For continuous safety variables, the change from baseline was tested with the same step-down method as that used for the efficacy variables. For categoric safety variables, the *P* value was based on the Cochran-Mantel-Haenszel test adjusted for baseline covariates (age, sex, diabetes, and metabolism of nebivolol. AEs were also analyzed by combining all active-treatment patients and comparing them with the placebo group.

Sample characteristics: A total of 568 patients were screened; 83 patients failed screening and 485 patients continued in the single-blind phase. The ITT population consisted of 49, 49, 50, 51, 50, and 51 patients who took at least one dose of placebo or nebivolol 2.5, 5, 10, 20, or 40 mg, respectively. A total of 259/300 (86.3%) patients completed the study; 83.7% in the placebo group and 86.95 in the nebivolol groups combined.

Compliance behavior: Patient compliance is shown in **Table 10**.

Table 10. Patient Compliance in Study NEB-202 (Population: Intent-to-Treat)

Statistic	Placebo	Nebivolol 2.5 mg n (%)	Nebivolol 5 mg n (%)	Nebivolol 10 mg n (%)	Nebivolol 20 mg n (%)	Nebivolol 40 mg n (%)
N	45	46	42	49	50	47
Compliance[a,b]	39 (86.7)	42 (91.3)	41 (97.6)	48 (98.0)	42 (84.0)	43 (91.5)
Non-compliance	6 (13.3)	4 (8.7)	1 (2.4)	1 (2.0)	8 (16.0)	4 (8.5)
Mean (SD)	96.2 (5.8)	96.4 (4.7)	97.7 (4.9)	97.8 (3.1)	94.4 (8.5)	96.5 (5.7)
Median	99.0	97.7	98.8	100.0	97.6	98.8
Range	(73.6, 100.0)	(79.1, 100.0)	(69.9, 100.0)	(87.1, 100.0)	(60.6, 100.0)	(77.6, 100.0)

(a) A patient is compliant if 90% or more scheduled doses were taken.

(b) *P* = 0.090 (Chi-Square Test).

Note: If any bottle was not returned or the number of pills returned not recorded, then the patient will be excluded from the overall compliance. Compliances greater than 100% were set to 100%.

Generalizability of population treated: This study was conducted exclusively in blacks and therefore its generalizability would be limited to this racial group. Nevertheless, this was an important study, as blacks are affected disproportionately by hypertension.[17]

CSR NEB-306

Reference citation: Sherry JH, Miller AB. A Multi-Center, Parallel Group Extension Study to Determine the Safety and Efficacy of Long-Term Nebivolol Exposure in Patients With Mild to Moderate Hypertension (Final Report), Bertek Pharmaceuticals Inc. Clinical Study Report NEB-306, Morgantown, West Virginia, March 2004.[71]

Principal findings

9-Month Extension Phase

- Nebivolol at daily doses ranging from 5 mg to 20 mg remained effective during long-term use (3 months in NEB-302, NEB-305, or NEB-202, plus 9 months [extension phase] in NEB-306) in patients with mild to moderate hypertension with or without adjunct diuretic or CCB therapy.
- At all time points (days 28, 91, 182 and 273 of the extension phase), significant mean decreases from baseline (ie, baseline in the feeder study) in trough sitting DBP were observed in the nebivolol and nebivolol + diuretic treatment groups, with larger decreases observed for the nebivolol group (-12.3 mm Hg on day 28, -14.6 mm Hg on day 91, and -15.0 mm Hg on days 182 and 273) than the nebivolol + diuretic group (-5.0 mm Hg on day 28, -7.1 mm Hg on day 91, -10.7 mm Hg on day 182, and -12.0 mm Hg on day 273).
- Similar decreases were achieved in sitting SBP at trough (-14.8 mm Hg in the nebivolol group).
- The reductions in DBP and SBP were supported by significant reductions in standing and supine DBP and SBP at trough as well as sitting, standing, and supine DBP and SBP at peak.
- Protocol-defined adjunct therapy was required for less than a third of the patients, with 26.8% receiving diuretic and 2.5% receiving CCB in combination with nebivolol. Few (1.1%) patients required rescue medication, defined as nebivolol once daily plus one adjunct therapy, such as a diuretic (or diuretic-like), CCB, or one other antihypertensive medication, and at least one additional anti-hypertensive therapy.
- Overall, 74.0% of patients were responders (DBP at end of study <90 mm Hg or decreased by $\geq$10 mm Hg from baseline to end of study). The group with the highest percentage of responders was the nebivolol group (78.2%), followed by the nebivolol + other group (72.7%) and the nebivolol + diuretic group (65.5%). The treatment group with the lowest percentage of responders was the nebivolol + CCB group (40.0%).
- Nebivolol was well tolerated and there were no unexpected changes in the types of AEs during the 9-month extension phase.
- The incidence of AEs over the 9-month extension phase was 54.6% (compared to 45.0%, 46.1%, and 42.5% in feeder studies NEB-202, NEB-302, and NEB-305, respectively).

- The AEs with the highest incidences were headache (5.4%) and fatigue (4.6%).
- There were no deaths reported in this study. Seventeen (2.0%) patients experienced 19 SAEs, of which 2 were considered treatment related (severe right upper quadrant pain and impotence).
- No patient had a clinically significant (as defined per protocol) laboratory abnormality associated with cardiovascular risk, ie, total cholesterol, LDL, high-density lipoprotein (HDL); or triglycerides. Mean glucose levels increased from baseline in the nebivolol monotherapy group on day 182 only (mean change 3.26 mg/dL), but the change was not clinically meaningful.

4-Week Follow-Up Phase

- Based on the observed efficacy data in the 4-week follow-up, which was included in this study to assess the effect of abrupt withdrawal of therapy and to provide evidence of long-term efficacy of nebivolol, rebound hypertension does not appear to be a concern with discontinuation of nebivolol.
- 18 patients received placebo, and consequently were withdrawn from nebivolol therapy. In this group, DBP and SBP in the sitting, standing and supine positions increased over the 28-day follow-up period, but did not return to baseline levels. The percent of placebo responders at the end of the follow-up phase (72.2%) was similar to the responder rate at the end of the extension phase for patients who received nebivolol monotherapy (78.2%).
- Not unexpectedly, there were heart rate increases of 5 to 8 bpm in the patients who withdrew from nebivolol.
- The patients who were randomized to placebo experienced no SAEs, had no discontinuations due to AEs, and reported only 1 severe AE, a spontaneously resolving episode of vertigo. In these placebo patients, other than the aforementioned heart rate increases, the withdrawal of antihypertensive medication was not associated with any observable risk.

Implications of study findings

- In this study, nebivolol continued to be effective for treatment of mild to moderate hypertension. The consistent reductions in blood pressure achieved with nebivolol monotherapy throughout the 9-month extension phase indicate that a sizeable proportion of patients who responded initially to nebivolol monotherapy continued to respond to monotherapy.
- The smaller blood pressure reductions in the nebivolol + diuretic group compared to the monotherapy group that occurred at earlier study visits illustrate the rationale for use of the adjunct therapy, ie, patients who either met the criteria for adjunct therapy, or for whom the investigator

believed blood pressure control was not adequate, were given adjunct therapy in an attempt to decrease blood pressure further.
- Results of the 4-week follow-up phase of this study showed that rebound hypertension did not appear to be a concern with discontinuation of nebivolol.
- Nebivolol was well tolerated as both monotherapy and with adjunct therapy. No patient had a clinically significant laboratory abnormality associated with cardiovascular risk.

Study Population: Male and female patients aged 18 years or older who successfully completed NEB-202, NEB-302, or NEB-305 were eligible to participate in the study. Patients were not included if they had secondary or malignant hypertension; BMI $\geq$40 kg/m^2; bronchospasm, bradycardia, or any other known contraindication to beta blocker therapy; uncontrolled diabetes mellitus (hemoglobin A_{1c} $\geq$10%); recent (within 6 months) myocardial infarction or stroke; heart failure; hemodynamically significant valvular heart disease; clinically significant thyroid, renal, or hepatic dysfunction; peripheral vascular disease; positive pregnancy test result; previous exposure to nebivolol; or concomitant therapy with at least 1 prohibited or restricted medication that may have affected BP (eg, all antidepressants with BP-altering effects, including tricyclic antidepressants and monoamine oxidase inhibitors).

Study Design and Procedures: This multi-center, phase 3, parallel-group, 9-month extension study was conducted at 123 sites in the United States and Europe from March 2002 (date of first enrollment) to September 2003 (date last patient completed study).

This study enrolled patients completing one of three feeder studies NEB-302, NEB-305, and NEB-202; this study also had a 4-week follow-up phase to assess the possibility of a rebound effect. The 4-week follow-up phase was open to patients who completed the extension phase (either by completing the last visit or early discontinuation visit) and received only nebivolol monotherapy during the extension phase. In the follow-up phase, the patients were randomized to double-blind treatment in a 2:1 ratio of placebo and nebivolol.

In the 9-week extension phase of this study, patients received nebivolol once daily (5, 10, or 20 mg) as monotherapy or with adjunct therapy, where the adjunct therapy was defined as an open-label thiazide/thiazide-like diuretic, or thiazide/thiazide-like diuretic with triamterene or amlodipine 5 or 10 mg. No patients received placebo in this phase of the study. The dose of nebivolol and the possible addition of adjunct therapy were to be determined from an algorithm based on a patient's sitting trough DBP and heart rate and the nebivolol dose assigned at the previous study visit. Titration of nebivolol and adjunct therapy were permitted at some visits.

There were 5 study visits during the extension phase, ie, the last study visit of the feeder study (day 0 in this study) and 4 additional visits (day 28, 91, 182, and 273). During the 4-week follow-up phase, there were 3 study visits (follow-up days 7, 14, and 28) after the last study visit of the extension phase.

Primary and Secondary End Points: The primary efficacy end point was change at the end of the extension phase compared with baseline from NEB-202, NEB-302, or NEB-305 in mean SiDBP at trough (24±2 hours post-previous morning's dose). Secondary efficacy end points included changes at the end of the extension phase compared with baseline from NEB-202, NEB-302, or NEB-305 in mean SiSBP at trough, mean SiDBP and SiSBP at peak (2-3 hours postdose), and mean supine and standing DBP and SBP at trough and peak. In addition, response rates of treatment groups were obtained (a responder was defined 2 ways in this study: 1) to be consistent with the feeder studies, as a patient whose sitting DBP [trough] at the end of the study was <90 mm Hg or was decreased by ≥10 mm Hg from baseline [ie, baseline from NEB-202, NEB-302, or NEB-305] to the end of treatment; and 2) per protocol, as a patient whose average sitting DBP [trough] at the end of the study was <90 mm Hg), as well as the effect of nebivolol over time (BP parameters and percent of responders were plotted over time) and incidences of patients who received rescue medication for BP during the extension phase.

Efficacy and Safety Assessments: BP was measured at trough and peak using an automatic sphygmomanometer and appropriately sized cuff in the supine, sitting, and standing positions. Three separate measurements were taken 2 minutes apart in the same arm: first after the patient had been at rest in the supine position for at least 5 minutes, then after sitting for 1 minute, and finally after standing for 1 minute. The mean of 3 readings in each position was calculated and recorded. Trough BP and heart rate measurements were taken at all visits; peak BP and heart rate measurements were taken at all extension-phase visits except the day 28 visit (and were not taken during the 4-week follow-up). Safety was assessed by clinical review, vital signs (including heart rate), 12-lead ECGs, and clinical laboratory evaluations including chemistry panel, hematologic profile, and urinalysis. All AEs occurring during the study were documented as to type, onset, duration, intensity, and relation to study drug.

Statistical methods: The cohort of patients in this study was self-selected; therefore, no formal statistical comparisons were performed. Descriptive statistics (mean, standard error [SE], and 95% confidence intervals [CIs]) were summarized for all continuous efficacy parameters. The incidences of patients with at least 1 AE while on nebivolol in the NEB-306 extension phase were summarized by counts and percentages. Categorical safety parameters were summarized by counts and percentages. BP parameters were displayed over time.

Sample characteristics: There were 845 patients in this extension study; 550 patients received nebivolol (with or without adjunct therapy) for at least 6 months and 282 patients received nebivolol for at least 9 months.

Compliance behavior: Patient compliance is shown in **Table 11** and **Table 12**.

Table 11. Patient Compliance in Study NEB-306 (Population: Intent-to-Treat), 9-Month Extension Phase

Statistic	Placebo	Nebivolol 5 mg n (%)	Nebivolol 10 mg n (%)	Nebivolol 20 mg n (%)
N	560	199	21	10
Compliance[a]	531 (94.8)	183 (92.0)	21 (100.0)	10 (100.0)
Non-compliance	29 (5.2)	16 (8.0)	0	0
Mean (SD)	97.5 (6.4)	96.8 (7.0)	98.2 (2.9)	98.0 (2.6)
Median	99.6	99.3	100.0	98.7
Range	(12.5, 100.0)	(43.6, 100.0)	(91.4, 100.0)	(91.1, 100.0)

(a) A patient is compliant if 90% or more scheduled doses were taken.

Note: If any bottle was not returned or the number of pills returned not recorded, then the patient will be excluded from the overall compliance. Compliances greater than 100% were set to 100%.

Table 12. Patient Compliance in Study NEB-306 (Population: Intent-to-Treat), 4-Week Follow-Up Phase

Statistic	Placebo	Nebivolol 5 mg n (%)	Nebivolol 10 mg n (%)	Nebivolol 20 mg n (%)
Compliance[a]	18 (100.0)	5 (100.0)	4 (100.0)	1 (100.0)
Non-compliance	0	0	0	0
N	18	5	4	1
Mean (SD)	98.6 (2.6)	100.0 (0.0)	99.1 (1.9)	100.0 (N/A)
Median	100.0	100.0	100.0	100.0
Range	(92.6, 100.0)	(100.0, 100.0)	(96.3, 100.0)	(100.0, 100.0)

(a) A patient is compliant if 90% or more scheduled doses were taken.

Note: If any bottle was not returned or the number of pills returned not recorded, then the patient will be excluded from the overall compliance. Compliances greater than 100% were set to 100%.

Generalizability of population treated: The majority of patients were male (53.4%). Most patients were <65 years of age (83.1%), nonblack (76.7%), and not diabetic (93.7%). The majority of patients (58.0%) had a BMI <30kg/m^2. Therefore, the patients studied can be regarded as representative of the general U.S. hypertensive population.[94-97]

Demographics and other baseline characteristics for patients entering the 4-week follow-up phase were similar to those of patients in the 9-month extension phase, except that the majority of patients in the follow-up phase were female (75.0%) compared with 46.6% in the 9-month extension phase.

CSR NEB-321

Reference citation: Sherry JH, Miller AB. A Double-Blind, Multi-Center, Randomized, Placebo-Controlled, Parallel Group Study of the Efficacy and Safety of Nebivolol Added to Existing Antihypertensive Treatment in Patients with Mild to Moderate Hypertension, Bertek Pharmaceuticals Inc. Clinical Study Report NEB-321, Morgantown, West Virginia, March 2004.[70]

Principal findings

- Once-daily nebivolol, when added to a variety of background antihypertensive treatment regimens (at least 1 and no more than 2 of an ACEI, ARB, and/or diuretic), was well tolerated, provided significant additional reductions in BP (which were maintained throughout the 24-hour period), and improved response rates in patients with uncontrolled hypertension.
- The following BP results are presented as LS mean values.
- Addition of once-daily nebivolol 5, 10, or 20 mg to ongoing antihypertensive therapy produced statistically significant mean reductions in trough SiDBP of -6.6, -6.8, and -7.9 mm Hg, respectively, versus -3.3 mm Hg for placebo (P <0.001).
- The corresponding values for trough SiSBP were -5.7, -3.7, and -6.3 mm Hg, respectively, versus -0.1 mm Hg for placebo ($P \leq 0.015$).
- The significant incremental reductions in BP in the nebivolol treatment groups, compared with placebo, were apparent by Week 2 (first assessment following randomization) and were sustained throughout the remainder of the 12-week treatment period.
- All doses of nebivolol also significantly reduced peak SiDBP and SiSBP at Week 12, compared with placebo, with reductions from baseline of up to -13.6 mm Hg and -13.3 mm Hg, respectively (P <0.001 for both SiDBP and SiSBP, all doses vs placebo). Reductions from baseline to Week 12 in trough and peak BP with nebivolol in both supine and standing positions were consistent with those for SiDBP and SiSBP.
- Nebivolol 5 to 20 mg also significantly reduced mean 24-hour ambulatory BP (P <0.001 for SiDBP and $P \leq 0.005$ for SiSBP vs placebo for all doses).
- Addition of nebivolol 5 to 20 mg resulted in significantly more responders (SiDBP <90 mm Hg or $\geq$10 mm Hg reduction), with a range of 53.0% to 65.1% vs 41.3% with placebo ($P \leq 0.028$). Nebivolol was also associated with significantly better control rates (patients achieving SiSBP/SiDBP <140/90 mm Hg), which ranged from 41.3% to 52.7% vs 29.3% with placebo ($P \leq 0.029$).
- Addition of nebivolol to background antihypertensive therapy resulted in statistically significant reductions from baseline to the end of the study in mean trough sitting heart rate compared with placebo. The mean

reductions were -7.3, -7.6, and -10.6 bpm for nebivolol 5, 10, and 20 mg, respectively, versus -3.0 bpm for placebo (*P* <0.001 for all doses).

- Nebivolol was well tolerated, with an overall incidence of treatment-emergent AEs that was comparable to that of placebo (40.2% vs 38.9%, respectively; *P*=0.763).
- The most frequently-reported AEs in patients treated with nebivolol were headache (5%), fatigue (3.6%), urinary tract infection (3.2%), dizziness (2.4%), and nasopharyngitis (2.2%). No individual AEs occurred at a significantly higher incidence among patients treated with nebivolol compared with placebo-treated patients.
- In addition, the incidence rates of AEs commonly associated with beta blocker use were very low in the combined nebivolol groups versus placebo, including bradycardia (0.8% vs 0.0% for nebivolol and placebo groups, respectively), decreased libido (0.4% vs 0.0%) or unspecified sexual dysfunction (0.0% vs 0.6%), and depression (0.2% vs 0.0%).
- Adverse events of severe intensity were reported in 2.4% of placebo-treated patients and 2.2% of patients in the combined nebivolol groups, and were not related to nebivolol dose (nebivolol 5 mg, 3%; 10 mg, 1.2%; 20 mg, 2.4%). There was 1 death during the study. A 75-year-old female died with cardiac arrest in the nebivolol 5 mg dose group. This was judged by the investigators to be remotely related to study drug.
- Seven patients (3 in the placebo group and 4 in the nebivolol group) reported 11 serious AEs, none of which were considered by investigators to be related to study drug.
- A total of 25 patients withdrew from the study due to AEs, including 4 (2.4%) in the placebo group and 21 (4.2%) of the patients treated with nebivolol. No dose relationship was observed for AEs leading to withdrawal (5.4% in the nebivolol 5 mg group, 3% in the 10 mg group, and 4.2% in the 20 mg group).
- For most laboratory parameters associated with cardiovascular risk (total cholesterol, LDL-C, triglycerides, and glucose), there were no significant changes, except for small but statistically significant reductions in HDL-C (mean decrease from 1.3 to 2.5 mg/dL, with no dose relationship).

Implications of study findings

- This study demonstrates that once-daily nebivolol added to a variety of background antihypertensive treatment regimens is an effective, safe, and well tolerated treatment option for patients with uncontrolled hypertension despite therapy.
- Nebivolol as add-on therapy provided greater statistically significant decreases in mean 24-hour ambulatory BP (both DBP and SBP) than placebo, confirming the findings from mean sitting BP measurements and indicating the robustness of the study findings.
- Addition of nebivolol increased the BP responder rate with tolerability comparable to placebo across a diverse population of U.S. patients.

- Nebivolol demonstrated neutral metabolic effects, a finding which may further support the use of nebivolol in a wide range of hypertensive patients, including those with metabolic disturbances.
- The additional BP lowering provided by nebivolol as add-on therapy has the potential to reduce the risks associated with uncontrolled hypertension. Furthermore, the antihypertensive efficacy of nebivolol add-on therapy, coupled with a favorable tolerability profile, addresses 2 issues fundamental to achieving successful BP control, sufficient therapy and patient adherence to therapy.

Study Population: Men and women, aged 18 years or older, with mild to moderate hypertension (clinic SiDBP ≤90 mm Hg and ≤109 mm Hg) at screening and baseline, while on a stable regimen of antihypertensive medications consisting of at least 1 and no more than 2 of an angiotensin-converting enzyme inhibitor (ACEI), angiotensin receptor blocker (ARB), or diuretic. Exclusion criteria were BMI >35 kg/m^2, malignant hypertension, bradycardia, respiratory disorders, cardiac arrhythmias, uncontrolled type 2 diabetes mellitus (hemoglobin A_{1c} >10% at screening), clinically significant hepatic or renal dysfunction, myocardial infarction or cerebrovascular disease in the last 6 months, heart failure requiring treatment, significant valvular heart disease, severe peripheral vascular disease, intolerance to beta blockers, or previous exposure to nebivolol for the treatment of hypertension.

Study Design and Procedures: This randomized, double-blind, placebo-controlled, parallel-group study was conducted at 96 sites in the United States from October 2002 (date of first enrollment) to October 2003 (date last patient completed study).

The study design comprised a screening/washout phase followed by randomization/treatment for 12 weeks. Patients taking a permitted stable regimen of antihypertensive medications underwent a screening assessment that included a complete medical history, physical examination, clinic BP and heart rate measurement, safety laboratory tests (blood hematology, blood chemistry and urinalysis), genomics testing, and 12-lead electrocardiography. Patients taking beta blockers at screening underwent a 14 ± 3-day washout prior to baseline.

At baseline (day 1), demographic and baseline clinical characteristics, including clinic BP measurement, heart rate, 24-hour ambulatory blood pressure monitoring (ABPM), and 12-lead ECG were recorded, and eligible patients were randomized to receive once-daily (in the morning) double-blind treatment with concomitant nebivolol 5, 10, or 20 mg or placebo for 12 weeks. Patients returned to the study unit for assessments on days 14, 42, and 84 of the double-blind treatment period, at which time BP and heart rate were measured, compliance with study medication was monitored, and use of concomitant medications was

recorded. The 24-hour ABPM, 12-lead ECG, and laboratory assessments were repeated at Week 12 (day 84).

Concomitant therapy with oral and ophthalmic beta blockers, CCBs, α_1-receptor blockers, and long-acting oral nitrates was prohibited during the single-blind run-in phase and during the double-blind treatment period.

Primary and Secondary End Points: The primary efficacy endpoint was the change from baseline to day 84 in mean clinic SiDBP at trough (24 ± 3 hours post-previous morning's dose). Secondary efficacy endpoints included changes from baseline to day 84 in mean trough SiSBP, mean SiSBP and SiDBP at peak (2–3 hours post-dosing), mean peak and trough supine and standing SBP and DBP, and mean 24-hour DBP and SBP as measured by ABPM. Another efficacy variable was the responder rate of treatment groups, defined as the proportion of patients with a SiDBP of <90 mm Hg at the end of the study or an absolute reduction of ≥10 mm Hg in SiDBP from baseline. Additional objectives were to assess the safety and tolerability of nebivolol.

Efficacy and Safety Assessments: Blood pressure was measured using a calibrated standard sphygmomanometer and appropriately sized cuff. Measurements were taken at trough and peak drug concentration in the supine, sitting, and standing positions. Three separate measurements were taken in each position 2 minutes apart in the same arm – after the patient had been at rest in the supine position for at least 5 minutes, then after sitting for 1 minute, and finally, after standing for 1 minute. The average of the 3 readings in each position was used for analysis. Trough BP and heart rate measurements were taken at screening and randomization, and on days 14, 42 and 84 of the treatment period; peak BP and heart rate measurements were taken at randomization, and on days 42 and 84 of the treatment period.

Noninvasive ABPM was carried out using a device calibrated to within 5 mm Hg of the mean of 3 DBP measurements taken using a standard sphygmomanometer, and validated independently by the American Association for the Advancement of Medical Instrumentation. During the monitoring period, patients recorded in a diary the exact time at which study medication was taken (bedtime, time of awakening and arising). At baseline and on day 84, 24-hour ambulatory BP was measured every 20 minutes during daytime hours (0600–2200), and every 30 minutes during night-time hours (2200–0600). The ABPM recording was accepted if it included at least 24 hours of recording following administration of a dose, had at least 60 valid readings (80% acceptance rate), and had no more than 2 nonconsecutive hours of missing data.

Safety was assessed by monitoring AEs, physical examination, body weight, ECG, and laboratory evaluation, including chemistry panel, hematologic profile and urinalysis.

Statistical methods: The ITT population, which included all randomized patients who took at least 1 dose of study drug, was the primary population for efficacy and safety analyses. Missing values were imputed using the last-observation-carried-forward method. All statistical tests were 2-sided at the 5% level of significance.

For demographic and baseline characteristics, continuous variables were compared among treatment groups using an ANOVA model, and categorical variables were compared using the Chi-square test.

Changes in BP from baseline to study end (day 84) were analyzed using an ANCOVA model, with study treatment, race, age, sex, diabetes status, predicted metabolism of nebivolol (extensive metabolizer vs poor metabolizer), and use of ACEI, ARB, and diuretic as factors in the model, and baseline measurement as a covariate. For pairwise comparisons between each of the 3 nebivolol treatment groups and placebo, the *P* values were adjusted using Hochberg's hierarchical step-up procedure. Pairwise comparisons with 95% confidence intervals were also performed for each nebivolol dose group and placebo. In addition, the proportion of patients defined as responders (SiDBP <90 mm Hg or ≥10 mm Hg reduction from baseline) between each nebivolol treatment group and placebo were analyzed using a logistic regression model with responder as the response variable and baseline DBP and dichotomous variables as covariates. The percentage of patients achieving BP control (SiDBP <90 mm Hg and SiSBP <140 mm Hg) at study end at each nebivolol dose was analyzed *post hoc* and compared with placebo using Pearson's Chi-square test.

For safety analyses, the Chi-square test was used to determine the overall effect of treatment on the distribution of AEs, and the Mantel-Haenszel test was used to determine the dose-trend effect. Laboratory parameters were compared statistically among treatment groups using ANOVA or ANCOVA (baseline as covariate).

Sample characteristics: A total of 1171 patients were screened, 502 of whom were ineligible for the double-blind treatment phase. Thus, 669 patients were randomized to receive either placebo or nebivolol, and all of them received at least one dose of study medication (the ITT population). A total of 598 patients (89.4%) completed the study: 146 patients (87.4%) in the placebo group and 452 (90%) in the nebivolol groups combined. There were no statistically significant differences between treatment groups at baseline with respect to use of background antihypertensive therapy.

Compliance behavior: Patient compliance is shown in **Table 13**.

Table 13. Patient Compliance in Study NEB-321 (Population: Intent-to-Treat)

Statistic	Placebo	Nebivolol 5 mg n (%)	Nebivolol 10 mg n (%)	Nebivolol 20 mg n (%)
N	167	168	168	166
Compliance[a]	132 (79.0%)	146 (86.9%)	141 (83.9%)	137 (82.5%)

(a) A patient is compliant if 90% or more scheduled doses were taken.

Generalizability of population treated: Treatment groups were comprised mainly of middle-aged and overweight hypertensive patients, approximately 55% of whom were men. Of the total study population, 29.4% were blacks and 14.1% had diabetes. Although there were more blacks in this study than in NEB-302 and NEB-305, the patients studied can be regarded as representative of the general U.S. hypertensive population.[94-97]

Special Analyses: Nebivolol Efficacy in Black Patients Studied in the Clinical Trials

Hypertension affects blacks disproportionately. In addition, the available data suggest that black patients respond differently than nonblack patients to some hypertension treatments. The study NEB-202, which was conducted only in black patients, demonstrated that nebivolol effectively reduced DBP and SBP and that BP control rates achieved in this study were comparable to those achieved with monotherapy in the general hypertensive population.[8] Relevant pooled analyses also have been conducted and are provided below:

Pooled analysis of 302/305 black patients only: Efficacy data from only the black patients in NEB-302 and NEB-305 were pooled for an additional independent confirmation of antihypertensive efficacy in these patients.[68] Baseline-subtracted mean changes in the primary endpoint, trough SiDBP, for nebivolol doses 2.5 to 40 mg, ranged from -6.3 to -10.0 mm Hg compared with -2.9 mm Hg for placebo,supporting the results from NEB-202. For trough sitting SBP, baseline adjusted mean changes for nebivolol doses 5 to 40 mg ranged from -4.2 to -12.4 mm Hg compared with -1.1 for placebo. But these results were not statistically significant compared with placebo.

Pooled analysis of 202/302/305 black patients only: The results of NEB-202 were combined with the pool of black patients from NEB-302 and NEB-305 and included a total population of 537 black patients who participated in the 3 placebo-controlled monotherapy studies.[68] Mean reductions from baseline in trough SiDBP, the primary endpoint, were significant ($P \leq 0.036$) for all dose ranges tested compared to placebo. The baseline-subtracted mean changes were -8.8, -6.6, -8.4, -8.6, -7.5 and -9.2 mm Hg for the nebivolol 1.25 mg (n=12), 2.5 mg, 5 mg, 10 mg, 20 mg and 40 mg dose groups, respectively, compared with -3.3 mm Hg for placebo. However, for trough sitting SBP, the baseline-subtracted mean changes for all nebivolol doses compared to placebo were not significant. The reductions were -9.9, -2.7, -5.6, -6.3, -5.6 and -7.5 mm Hg for the nebivolol 1.25 mg, 2.5 mg, 5 mg, 10 mg, 20 mg and 40 mg dose groups, respectively, compared with -1.4 mm Hg for placebo. In conclusion, pooled data from NEB-202, NEB-302, and NEB-305 support nebivolol as an effective antihypertensive agent in blacks.

Pooled analysis of obese patients:

The blood pressure data from obese patients enrolled in the three U.S. registration trials were pooled for analysis.[68] Obesity was defined as a body mass index of $\geq$30 kg/m^2. The data for patients who were randomized to placebo or to nebivolol 5, 10 or 20 mg once daily demonstrated significant BP reductions after nebivolol therapy. The number of patients in each treatment group ranged from 92 in the placebo group to 196 in the nebivolol 20 mg once daily group.

After 3 months of double-blind therapy, there were significant, dose-related decreases in blood pressure in obese patients treated with nebivolol. DBP reductions ranged from -4.8 mm Hg in the placebo group to -10.3 mm Hg in the nebivolol 10 mg group, and SBP reductions ranged from -3.6 in the placebo group to -10.9 mm Hg in the nebivolol 20 mg group.

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